MEDICAL SCIENCES

CONTRIBUTION TO THE STUDY OF "SMOKING AND RADON" INTERACTION IN THE LUNG CANCER DEVELOPMENT IN THE REPUBLIC OF MOLDOVA

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Keywords: *tobacco smoking, radon, lung cancer, cluster analysis.*

Introduction. *The major risk factors for lung cancer include tobacco smoking and exposure to residential radon. A comprehensive study was conducted in the Republic of Moldova to explore the interaction of smoking and radon as triggering factors for lung cancer morbidity.*
Material and methods. *The study used data on tobacco smoking prevalence from the national 2021 STEPS study, lung cancer morbidity data from 2012 to 2020, and radon measurements obtained through RADTRAK2 during 2018 and 2021. The data processing tools employed summary statistics and cluster analysis.*
Results. *The distribution of high radon values, the number of smokers and the lung cancer morbidity is uneven throughout the country. The formation of a larger cluster combining all variables developed from the formation of two distinct clusters: 1. the incidence and prevalence of lung cancer, the total number of tobacco smokers, the number of male smokers, the number of female smokers, and the number of urban smokers, 2. the radon concentration and the number of rural smokers.*
Conclusions. *The study results demonstrate the leading role of tobacco smoking on morbidity rate among adult population, regardless of gender across urban areas with a rather low radon concentration. At the same time, they indicate the cumulative effect of smoking and increased radon concentration in rural areas due to home construction features and lifestyle.*

Cuvinte-cheie: *fumat de tutun, radon, cancer bronhopulmonar, analiză clusteriană.*

CONTRIBUȚIE LA STUDIUL INTERACȚIUNII „FUMAT ȘI RADON" ÎN DEZVOLTAREA CANCERULUI BRONHOPULMONAR ÎN REPUBLICA MOLDOVA

Introducere. *Expunerile la fumul de tutun și la radonul rezidențial reprezintă factorii de risc major în dezvoltarea cancerului bronhopulmonar A fost efectuat un studiu care a avut în vizor interacțiunea fumat & radon ca factor declanșator al morbidității cancerului bronhopulmonar în Republica Moldova.*
Material si metode. *Au fost analizate datele privind prevalența fumatului din studiul național STEPS 2021, indicii vizând morbiditatea cancerului bronhopulmonar în 2012-2020 și rezultatele măsurătorilor concentrațiilor de radon obținute prin detectoare RADTRAK2 în 2018-2021. Instrumentele de prelucrare a datelor au inclus statistici rezumative și analiza clusteriană.*
Rezultate. *Distribuția valorilor sporite de radon, a numărului de fumători și a morbidității cancerului bronhopulmonar a fost neuniformă pe întreg teritoriul țării. Formarea unui cluster mare, care combină toate variabilele, derivă prin formarea a două alte clustere: 1. incidența și prevalența cancerului bronhopulmonar, numărul total de fumători de tutun, numărul de bărbați fumători, numărul de femei fumătoare și numărul de fumători din mediul urban; 2. concentrația radonului și numărul de fumători din mediul rural.*
Concluzii. *Rezultatele studiului demonstrează rolul principal al influenței fumatului asupra morbidității în rândul populației adulte, indiferent de sex, într-un mediu urban cu o concentrație diminuată de radon și, în același timp, indică asupra efectului cumulativ al fumatului și al valorilor sporite ale concentrației de radon în zonele rurale, din cauza caracteristicilor de construcție ale locuințelor și a stilului de viață.*

INTRODUCTION

Lung cancer (LC) is the most common cancer worldwide, as well as the most common cause of cancer-related death in men (1). In 2020, it ranked second as the most common cancer in the Republic of Moldova with over 726 people being diseased in the same year, thus, accounting for 8.5% of all newly diagnosed cancers in both men and women (2). Moreover, lung cancer is the second leading cause of death among the malignant tumors in the country (3, 4). The major risk factor contributing to the occurrence of LC is tobacco smoke, responsible for approximately 80% to 90% of all cases (5). Furthermore, the gas radon ranks among the other significant risk factors (6).

Radon (222Rn or Rn in further) is a natural noble gas with no smell, color, or taste, produced through the radioactive decay of uranium in the Earth's crust. While outdoor concentrations of Rn are generally low, they can accumulate indoors, particularly in houses, where the general population faces the highest exposure. Radon, being 7.5 times heavier than air, tends to concentrate in cellars, basements, and ground floors of buildings. However, cases of radon detection can also occur on the upper floors of residential and public buildings due to the "candle" effect. This phenomenon results from pressure differences between warm and cold air, causing the gas to rise. In homes, schools, and offices, radon levels can vary significantly, ranging from 10 Bq/m^3 to over 10,000 Bq/m^3. People might unknowingly live and work here in conditions with dangerously high radon concentrations, posing a serious threat to their health. Even minimal inhalation of radon and its short-lived decay products, which deposit in respiratory tracts and emit α-particles, can be hazardous to human health. These particles can cause damage to target organs, particularly the bronchial epithelium and tissue at the junctions of the respiratory tracts (7). The lower the radon concentration is in a house, the lower the risk of lung cancer is, as there is no known threshold below which radon exposure carries no risk. The risk of lung cancer occurrence increases by 16% per 100 Bq/m^3 with continued exposure to even average levels of radon concentration. This dose-response relationship is linear, meaning the risk of lung cancer proportionally increases with rising radon exposure (8). According to the World Health Organization (WHO) estimates, radon causes lung cancer in 3% to 14% of all cases, depending on the average level of radon concentration in the country and the prevalence of smoking (9, 10, 11). Moreover, the risk of LC development is significantly higher in smokers compared to non-smokers (11 – 14).

In many European countries a lot of studies of the assessment of the lung cancer risk associated with residential radon exposure have been conducted over several decades (10, 11, 15 – 19). It is possible to increase the statistical power of research results by combining information from several studies, but this is very difficult to do based on the published information. Urban areas tend to show lower radon concentrations than rural ones because a large number of people live high above ground in multi-storey buildings and the bedrock under the urban localities is usually sedimentary. Moreover, urban areas generally have a higher prevalence of tobacco smoking among population (10). Similar studies using multivariable logistic regression analysis methods were conducted in China (20). These studies revealed that exposure to incense smoke at home may elevate the risk of lung cancer among smokers, and concurrent exposure to radon may further increase this risk. A parallel statistical analysis in a Korean study produced results indicating that both residential radon and cigarette smoking were associated with increased odds of lung cancer. The difference in odds ratios (ORs) based on radon exposure was much more pronounced in smokers than in non-smokers (21).

Considering that lung cancer ranks second among total cancer morbidity and is also the second leading cause of death from malignant tumors in the Republic of Moldova (4), with more than a quarter of the adult population exposed to smoking (22) and radon posing an increased risk factor for public health in residential premises (23, 24), the *purpose of this study* is to assess the interaction between tobacco smoking and residential radon exposure in relation to lung cancer morbidity in the Republic of Moldova over the last ten years. The *research hypothesis* states that the use of statistical methods is a key tool for identifying and assessing the most vulnerable population groups to the cumulative effects of tobacco smoking and radon exposure as risk factors for lung cancer in the country.

Since the radon exposure is the second cause of lung cancer after tobacco smoking, obtaining the reliable relationships of their interaction is an important component in the rationale for the development and implementation of measures to control, mitigate and prevent the negative effect of radon on public health in the country.

MATERIAL AND METHODS

Radon concentration data, measured in the air of various house types (n=2500) across rural and urban areas in the main zones of the Republic of Moldova (North, Center, and South), between 2018-2021 by the National Agency for Public Health of the Republic of Moldova, have been used (25). The measurements mainly have been taken on the ground floor, in bedrooms or in living rooms. Long-term passive detectors, RADTRAK2 were used for the measurements, with an exposure period of 90 days. In 51% of homes, the radon concentration exceeded the national/European standard level of 300 Bq/m^3. Given the considerable variability in radon concentrations during measurements due to various factors, it is customary to use its arithmetic mean value in the scientific research.

Morbidity data on the incidence and prevalence of lung cancer per 100,000 of population (standardized index) disaggregated by gender, age and urban/rural residence in 2012-2020 have been provided by the Health Data Management Department of the National Agency for Public Health.

One of the important issues that emerged was the limited availability of data ***on number of smokers*** restricted to the whole country and only from a population study that had a limited number of interviewees, which poses several challenges when attempting to combine these data with regional radon measurement data and the lung cancer morbidity rates for the assessment. There-fore, a proportional extrapolation of the data on the number of tobacco smokers from the National Household Survey on non-communicable diseases (NCD) risk factor prevalence STEPS 2021 (total number of interviewees was 4097 people, age 18-69 y.o., both genders, urban/rural residence) has been carried out using the population data of the National Bureau of Statistics during this period (22, 26). The mathematical proportion between the total population number in each age group, gender and place of residence with the number of the population in the same categories by regions (rayons) has been calculated. Then, based on these proportional links, the number of smokers by region of the country has also been calculated. After that, a standardized number of smokers per 100,000 inhabitants has been calculated for further use in the study of *smoking x radon x lung cancer* associations (fig. 1).

Methods. Proportional extrapolation calculations were conducted within a created database in MS Access 2010. The spatial distribution of variables

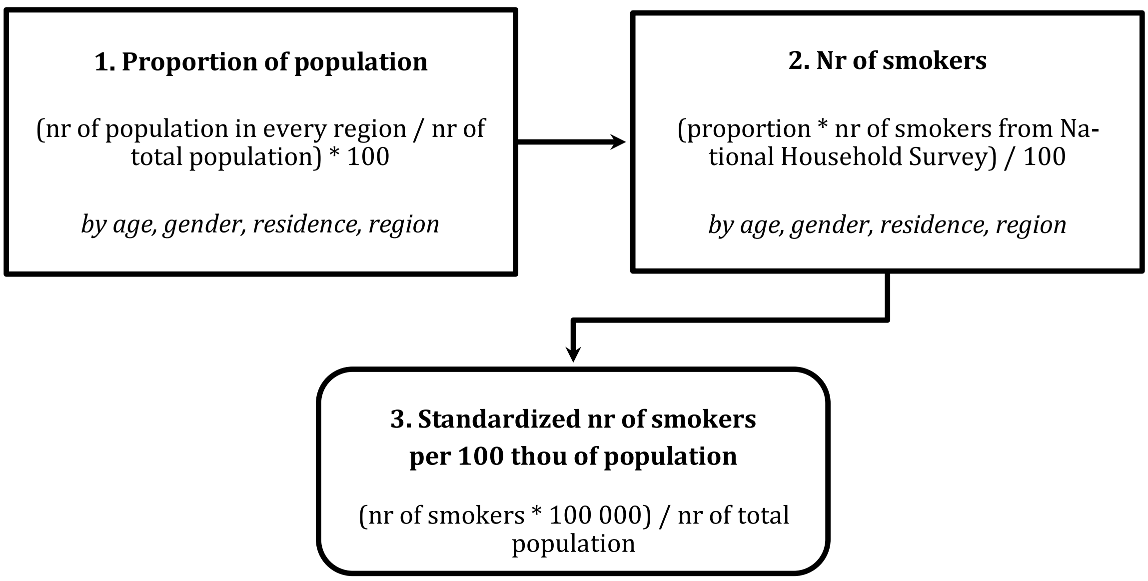


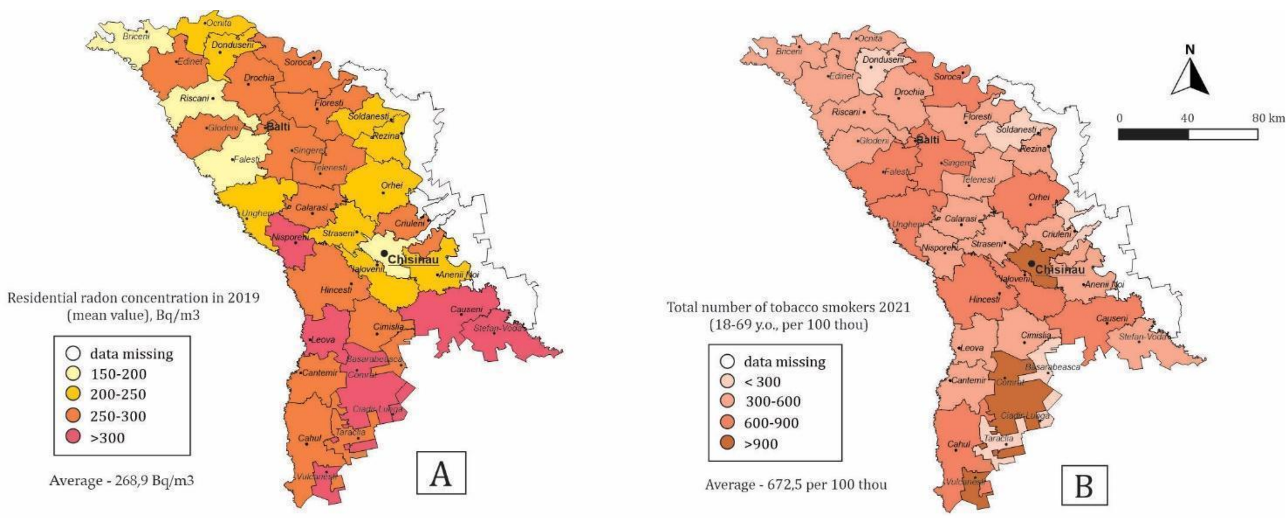
Figure 1. The proportional extrapolation algorithm used in the study.

as cartograms was performed using CorelDRAW 2020. Statistical analysis was performed using the specialized software Statgraphics Centurion XVIII, and the statistical toolkit included summary statistics of variables, such as the mean value, standard error, standard deviation, standardized kurtosis and asymmetry and cluster analysis. The use of statistical tools in such studies is quite widespread, being used to obtain reliable results within the medical and biomedical fields (11, 27).

RESULTS

According to the 2021 National Household Survey on the Prevalence of NCD Risk Factors (STEPS) (22), in the Republic of Moldova, 29.9% of the population are current tobacco users, with the prevalence about seven times higher among men (52.0%) than among women (7.7%). Smoking tobacco is far more common among men than women (48.9% vs 6.3%), are while women in urban areas are almost four times more likely to be current smokers than women in rural areas (10.0% vs 2.4%). The data, obtained through regional extrapolation, enabled us to create a spatial distribution of tobacco smokers. The spatial distribution of tobacco smokers by rayons is shown in Figure 2, B. The highest number of smokers is recorded in the Chisinau municipality (more than 5700 per 100 thou), while many rayons in the center of country show a fairly high number of smokers (600-900 per 100 thou). In the Autonomous Territorial Unit of Gagauzia the number of smokers is also higher than the national average. Spatial distribution (fig. 2, A) of radon measurements results in dwellings throughout the country demonstrates that the rayons along the Dniester and Prut rivers are relatively safe in terms of the national radon level (radon concentration 300 Bq/m^3), ranging 150-200 Bq/m^3, while the northern, southern and south-eastern rayons show radon concentrations over 250 Bq/m^3. Comparing the incidence and prevalence of lung cancer over a 10-year period (fig. 2, C and D) reveals that almost the same areas consistently indicate high values, particularly in the north, east, and southwest of the country.

The level of the lung cancer incidence (per 100,000) varies from year to year showing the highest rates observed in the North of the Republic of Moldova (fig.3). An analysis of lung cancer morbidity in recent years indicates that the highest incidence occurred in Donduseni rayon (50.1 per 100,000 in 2018), and the maximum prevalence was reported in Criuleni rayon (142.8 per 100,000 in 2017). Conversely, the lowest incidence and prevalence of lung cancer were registered in Cantemir rayon (8.0 per 100,000 in 2012) and Calarasi rayon (9.1 per 100,000 in 2017), respectively (28). Over the last three years, there has been a decrease in the LC incidence at the national level, and the 9-year linear trend demonstrates a slight decrease (it decreases by 0.14 per 100 thousand per year). On the other hand, lung cancer prevalence shows a modest increase, with a tendency of 0.3 per 100,000 per year. However, a slight decrease has been observed in the last three years, and the southern region of the country exceeded the central region in this parameter between 2018 and 2020. It is noteworthy that the maximum values of lung cancer prevalence were also recorded in the North of the country.



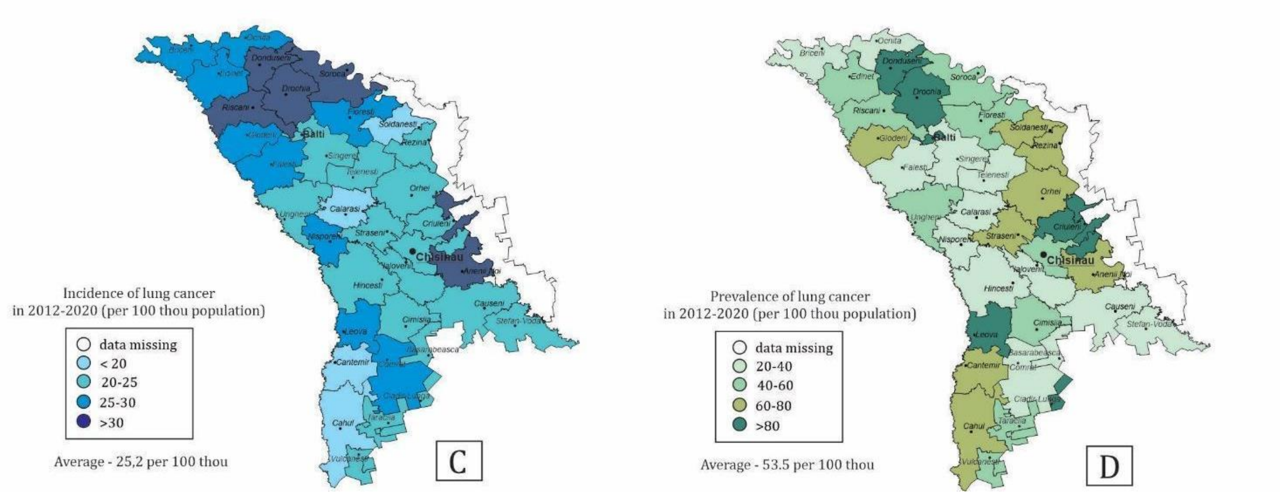


Figure 2. Cartograms of spatial distribution of radon concentration (A), total tobacco smokers (B), lung cancer incidence (C) and lung cancer prevalence (D) in the Republic of Moldova.

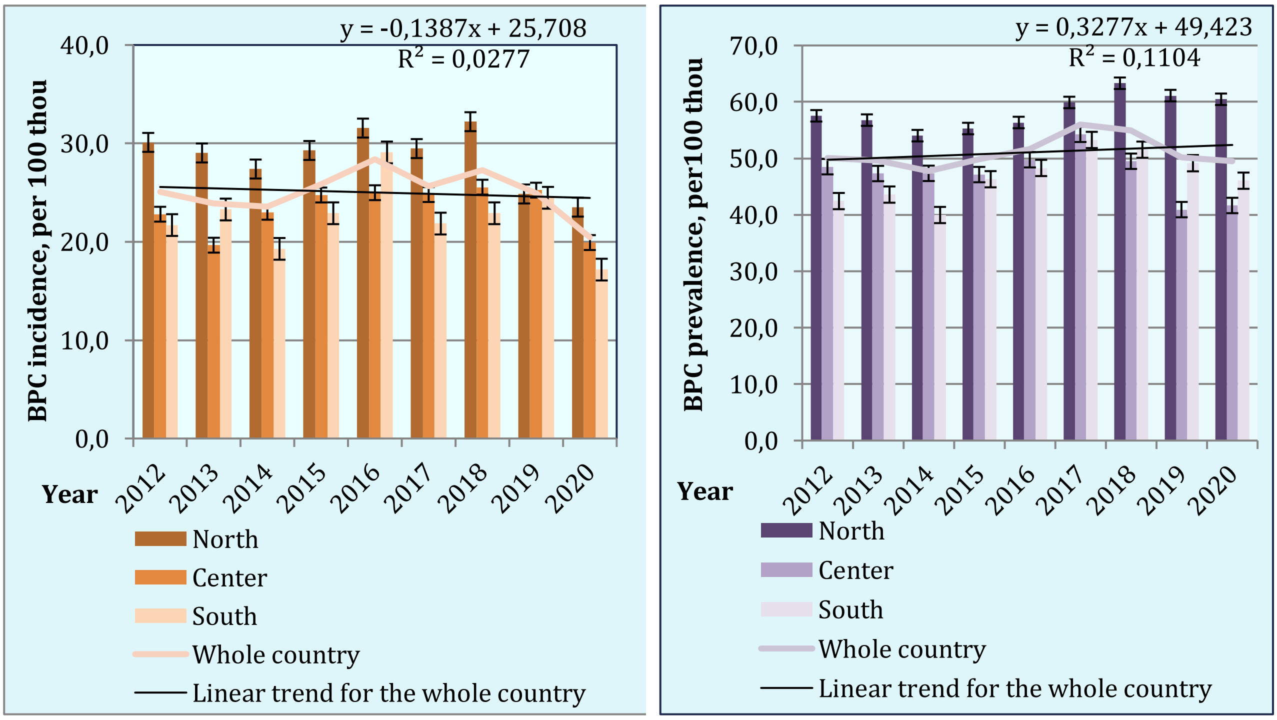


Figure 3. Incidence (left) and prevalence (right) of lung cancer (LC) in the Republic of Moldova (2012-2020) with linear trends and formulas *(R^2 - approximation confidence value).*

The descriptive-statistical analysis of the incidence and prevalence of lung cancer in the Republic of Moldova during the last 9 years is presented in Table 1. The standard error which estimates how the value of the statistic criterion changes from one sample to another for the LC incidence was small (~1), and it was even smaller across the country (0.8).

The standard error of lung cancer prevalence also indicates relatively small changes in relation to the average value in the regions, but when considering the entire country, it was even smaller at 3.5. However, the standard deviation for lung cancer incidence suggests average variability in the data (σ>2), while the standard deviation for prevalence was large (σ>19).

Average variability was further confirmed by the coefficient of variation (CV), which shows the proportion of the average spread of a random variable to the average value of this variable. For lung cancer incidence, this value was approximately 17%, with the smallest variation recorded in the northern part of the country. However, for lung cancer prevalence, the coefficient of variation was around 40%.

Table 1. Descriptive analysis of lung cancer morbidity, averaged over 2012-2020 (per 100 thousand).

Variable	Incidence				Prevalence			
	North	*Center*	*South*	*Whole country*	*North*	*Center*	*South*	*Whole country*
Mean	28.6	23.4	22.5	25.0	58.3	47.4	46.7	51.1
Standard error	1.0	1.1	1.2	0.8	6.7	5.1	6.4	3.5
Standard deviation (σ)	3.34	3.98	3.6	4.48	23.20	18.55	19.3	20.61
Coefficient of variation (CV), %	11.7	17.0	16.2	17.9	39.8	39.1	41.3	40.4
Minimum	22.1	19.2	17.5	17.5	32.7	20.9	26.2	20.9
Maximum	33.1	33.6	29.5	33.6	103.8	92.5	80.4	103.8

As shown, a direct comparison and an attempt to explain the relationship between smoking and radon with lung cancer morbidity, given the variability of these variables cannot be effectively carried out. To find this relationship, a statistically correct method was needed. The search for an appropriate method for assessing these risk factors must precede their statistical description, enabling an understanding of the nature of the variables under study. Table 2 provides data from a standard set of descriptive statistics on mean radon concentration, number of smokers, and LC morbidity in the country.

The coefficient of variation was quite high for the number of smokers, with a difference between the smallest and largest standard deviations exceeding 3 to 1, indicating significant heterogeneity. Of a particular interest are the standardized asymmetry and a standardized kurtosis, which can be used to determine whether the samples come from normal distributions. Values outside the range of -2 to +2 for tobacco smokers indicate considerable deviations from normality. This highlights a pronounced non-normality in the distribution of data, thereby challenging the assumption that the data originate from normal distributions.

Table 2. The statistical characteristics of the variables studied in the Republic of Moldova.

Variables	Statistic parameters						
	Average	*Median*	*Standard error*	*Standard deviation (σ)*	*Coefficient variation (CV), %*	*Standardized asymmetry*	*Standardized kurtosis*
Mean average Rn concentration, *Bq/m³*	261.8	262.8	9.62	56.1	21.4	1.51	1.73
Number of total tobacco smokers (per 100 thou)	685.3	525.0	156.14	910.4	132.8	12.89	36.52
Incidence of lung cancer (per 100 thou)	25.0	24.0	0.77	4.48	17.9	0.83	2.21
Prevalence of lung cancer (per 100 thou)	51.1	45.0	3.53	20.61	40.4	-1.04	0.33

Checking the normality of the distribution of the variables using the Shapiro-Wilks and Kolmogorov-Smirnov tests as statistically principal tools for this purpose (tab. 3), revealed that only the total number of smokers deviates from a normal distribution (criterion p≤0.05) with a confidence level of 95%. Conversely, the remaining indicators exhibit a significance value of≥0.05, affirming that these variables conform to a normal distribution. This analysis shows the heterogeneity of the variables, requiring the use of appropriate tools to investigate their subsequent interactions.

Table 3. Parameters used to test the normality of the distribution of the studied variables.

Variables	*p* - criterion Shapiro-Wilks	*p* - criterion Kolmogorov-Smirnov
Mean average Rn concentration, *Bq/m³*	0.169	0.746
Number of total tobacco smokers (per 100 thou)	3.37173E-11	0.000198146
Incidence of lung cancer (per 100 thou)	0.176424	0.64719
Prevalence of lung cancer (per 100 thou)	0.0220654	0.509546

To select an appropriate estimator for capturing the heterogeneity of variables, a multivariate analysis was conducted using the calculation of various statistics. The most appropriate method for this task, cluster analysis (a multivariate method), was employed, and the results are presented in Figure 4. Cluster analysis can be used as a tool for qualitatively assessing data that differs in nature but presumably has mutual associations a priori. For example, in our case, radon and smoking are considered trigger factors for the occurrence of lung cancer.

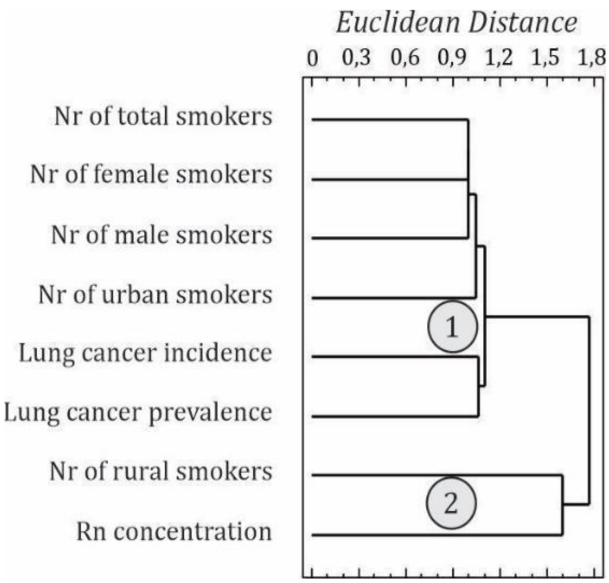


Figure 4. Dendrogram of the cluster analysis of the prevalence and incidence of lung cancer, the number of smokers and the concentration of radon in the Republic of Moldova.

A clustered multifactorial analysis was conducted to determine the Euclidean distances of the interactions among the studied parameters. The process began with the formation of a higher cluster (Euclidean Distance = 1.8), combining all variables, followed by the formation of two clusters with the smallest distances between variables, indicating their similarity: 1. The lung cancer incidence, the lung cancer prevalence, the number of total tobacco smokers, the number of male smokers, the number of female smokers and the number of urban smokers (Euclidean Distance = 1.1), 2. The radon concentration and the number of rural smokers (Euclidean Distance = 1.6).

DISCUSSIONS

The exposure to the residential radon is suspected to be a risk factor for lung cancer development, in addition to tobacco smoking, the carcinogenic potential of which is firmly established by more than three decades of evidence (12, 16, 29, 30, 31). So far, few studies have focused on the joint effect of tobacco smoking and residential radon on the occurrence of lung cancer. Only in the last 10 years, such studies have become more widespread due to the large amount of accumulated data and increased attention from the scientific community and public health bodies. A vast majority of these studies are based on case-control methods (32), with only a few being purely statistical and using multivariable logistic regression (20, 21). For example, in Slovenia, three data sources were recently associated at the level of settlements: lung cancer patients, residents, and the radon map of Slovenia (33). Analyzed using spatial smoothing models with Bayesian hierarchical models, it was found that about 60 people develop lung cancer every year due to radon exposure in the living environment, representing 5% of all individuals who develop this disease. An analysis of relative risk by gender showed that in Slovenia, an increased relative risk of lung cancer occurs in areas with higher radon exposure, mainly in men rather than in women. However, the lack of quantitative data on smoking in the statistical study limits its comprehensiveness, as it does not provide a complete assessment of the synergistic effect of smoking and radon in the development of lung cancer.

A limited number of statistical studies is primarily explained by the availability and accessibility of suitable data for such research across various categories, such as measuring radon concentration, tobacco smoking statistics, and lung cancer morbidity. Secondly, there are significant financial, human, and time costs associated with conducting such studies. While the results of case-control studies provide a closer understanding of the pathophysiological features of the *radon-smoking-cancer* interaction at the individual level, however, they have limitations in the regional and population aspects. Paradoxically, the statistical description of these associations at the regional and national levels serves more as a qualitative assessment than a quantitative one, which allows public health services to obtain an overall perspective on the public health problem, enabling them to adjust their policies to reduce the burden of diseases caused by tobacco smoking and natural ionizing radiation (6, 12).

Based on these considerations, this study attempts to statistically assess the association between lung cancer morbidity across the Republic of Moldova and both tobacco smoking and residential radon concentration. The distribution of high radon values, the number of smokers, and lung cancer morbidity is uneven throughout the country and does not always coincide, making it challenging to quantify the superposition of their interaction and the distribution of variables. Additionally, it is essential to provide a numerical expression of the number of tobacco smokers for statistical processing and analysis in this study, although the statistical extrapolation can be considered not as a quantitative but rather a qualitative assessment of the total number of smokers due to the uncertainties in the representativeness of the available data. In turn, this implies a qualitative assessment of the study results rather than a quantitative one. The use of statistical tools for the analysis of input data confirmed a heterogeneous variability of the variables and facilitated the selection of an appropriate assessment method. So far, cluster analysis of heterogeneous data has assisted in identifying arguments for the *smoking-radon-cancer* interaction. Formatted clusters, demonstrating the smallest Euclidean distances between risk factors and lung cancer morbidity, highlight the predominant role of tobacco smoking in the morbidity among the adult population, regardless of gender, in urban environments with relatively low radon concentrations. At the same time, these clusters indicate the interaction effect of smoking and increased radon concentration in rural areas, due to the construction features of houses and lifestyle (construction material, the presence of basements, living in one-story houses, etc.), aligning well with international studies (16, 21, 34).

CONCLUSIONS

1. To conclude, tobacco smoking remains a major public health problem worldwide as a major carcinogenic risk factor for radon-induced lung cancer. The combined concern of radon and smoking interaction presents a challenge for scientific research in this area. This analysis reveals a radon and tobacco smoking in the incidence and prevalence of lung cancer, manifesting in area-specific characteristics, i.e. abiotic and geogenic factors. The use of cluster analysis has allowed us to qualitatively assess the interaction of these factors on a regional scale. The association between tobacco smoking, radon and lung cancer morbidity has been confirmed nationwide through statistical analysis tools.
2. The availability of reliable results of such an assessment is an unconditional basis for developing and adopting appropriate preventive measures at all levels of the public health system and the health system as a whole. It is only natural that costly remedial actions to reduce indoor radon exposure should be based on a scientific risk assessment. Thus, there is a need in providing the strategic guidance on the synergistic approach to radon and tobacco control. This leads us to an important policy statement: reducing tobacco smoking among the population is the most cost-effective strategy for reducing the public health burden of radon exposure.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

FUNDING STATEMENT

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ETHICAL APPROVAL

The study does not need to be approved by the Ethics Committee because the initial data refer to public statistical data from yearbooks and databases of the National Bureau of Statistics and Health Data Management Department of the National Agency for Public Health collected and processed routinely, and the data about number of smokers are taken from the STEPS 2021 population study, which is based on the documented personal consent of the interviewees, and the results of which are also public.

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